ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Cetrotide 0.25 mg powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 vial contains:
0.26 - 0.27 mg cetrorelix acetate equivalent to 0.25 mg cetrorelix.

After reconstitution with the solvent provided, the concentration of cetrorelix is 0.25 mg/ml.

Excipients: 54.80 mg mannitol.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

Appearance of the powder: white lyophilized pellet
Appearance of the solvent: clear colourless solution

The pH of the reconstituted solution is 4.0 – 6.0

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prevention of premature ovulation in patients undergoing a controlled ovarian stimulation, followed by oocyte pick-up and assisted reproductive techniques.

In clinical trials Cetrotide 0.25 mg was used with human menopausal gonadotropin (HMG), however, limited experience with recombinant FSH suggested similar efficacy.

4.2 Posology and method of administration

Cetrotide 0.25 mg should only be prescribed by a specialist experienced in this field.

Cetrotide 0.25 mg is for subcutaneous injection into the lower abdominal wall.

The first administration of Cetrotide should be performed under the supervision of a physician and under conditions where treatment of possible pseudo-allergic reactions is immediately available. The following injections may be self-administered as long as the patient is made aware of the signs and symptoms that may indicate hypersensitivity, the consequences of such a reaction and the need for immediate medical intervention.

The contents of 1 vial (0.25 mg cetrorelix) are to be administered once daily, at 24 h intervals, either in the morning or in the evening. Following the first administration, it is advised that the patient be kept under medical supervision for 30 minutes to ensure there is no allergic/pseudo-allergic reaction to the injection. Facilities for the treatment of such reactions should be immediately available.

Administration in the morning: Treatment with Cetrotide 0.25 mg should commence on day 5 or 6 of ovarian stimulation (approximately 96 to 120 hours after start of ovarian stimulation) with urinary or

recombinant gonadotropins and is to be continued throughout the gonadotropin treatment period including the day of ovulation induction.

Administration in the evening: Treatment with Cetrotide 0.25 mg should commence on day 5 of ovarian stimulation (approximately 96 to 108 hours after start of ovarian stimulation) with urinary or recombinant gonadotropins and is to be continued throughout the gonadotropin treatment period until the evening prior to the day of ovulation induction.

For instructions on preparation , see section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance or any structural analogues of GnRH, extrinsic peptide hormones or to any of the excipients .
- Pregnancy and lactation.
- Postmenopausal women.
- Patients with moderate and severe renal and hepatic impairment.

4.4 Special warnings and precautions for use

Special care should be taken in women with signs and symptoms of active allergic conditions or known history of allergic predisposition. Treatment with Cetrotide is not advised in women with severe allergic conditions.

During or following ovarian stimulation an ovarian hyperstimulation syndrome can occur. This event must be considered as an intrinsic risk of the stimulation procedure with gonadotropins.

An ovarian hyperstimulation syndrome should be treated symptomatically, e.g. with rest, intravenous electrolytes/colloids and heparin therapy.

Luteal phase support should be given according to the reproductive medical centre´s practice.

There is limited experience up to now with the administration of Cetrotide 0.25 mg during a repeated ovarian stimulation procedure. Therefore Cetrotide 0.25 mg should be used in repeated cycles only after a careful risk/benefit evaluation.

4.5 Interaction with other medicinal products and other forms of interaction

In vitro investigations have shown that interactions are unlikely with medications that are metabolised by cytochrome P450 or glucuronised or conjugated in some other way. However, interactions with commonly used medicinal products, including products that may induce histamine release in susceptible individuals, may occur.

4.6 Pregnancy and lactation

Cetrotide 0.25 mg is not intended to be used during pregnancy and lactation (see section 4.3).

Studies in animals have indicated that cetrorelix exerts a dose related influence on fertility, reproductive performance and pregnancy. No teratogenic effects occurred when the drug was administered during the sensitive phase of gestation.

4.7 Effects on ability to drive and use machines

Due to its pharmacological profile cetrorelix is unlikely to impair the patient's ability to drive or to operate machinery.

4.8 Undesirable effects

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Immune system disorders	Rare (≥1/10,000, <1/1,000)	Rare cases of hypersensitivity reactions including pseudo-allergic/anaphylactoid reactions have also been reported
Nervous system disorders	Uncommon (≥1/1,000, <1/100)	Headache
Gastrointestinal disorders	Uncommon (≥1/1,000, <1/100)	Nausea
Reproductive system and breast disorders	Common (≥1/100, <1/10)	Mild to moderate ovarian hyperstimulation syndrome (WHO grade I or II) can occur which is an intrinsic risk of the stimulation procedure (see section 4.4).
	Uncommon (≥1/1,000, <1/100)	Severe ovarian hyperstimulation syndrome (WHO grade III)
General disorders and administration site conditions	Common (≥1/100, <1/10)	Local reactions at the injection site (e.g. erythema, swelling and pruritus) have been reported. Usually they were transient in nature and mild intensity. The frequency as reported in clinical trials was 9.4% following multiple injections of 0.25 mg cetrorelix.

4.9 Overdose

Overdosage in humans may result in a prolonged duration of action but is unlikely to be associated with acute toxic effects.

In acute toxicity studies in rodents non-specific toxic symptoms were observed after intraperitoneal administration of cetrorelix doses more than 200 times higher than the pharmacologically effective dose after subcutaneous administration.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: LHRH-Antagonist, ATC code: H01CC02.

Cetrorelix is a luteinising hormone releasing hormone (LHRH) antagonist. LHRH binds to membrane receptors on pituitary cells. Cetrorelix competes with the binding of endogenous LHRH to these receptors. Due to this mode of action, cetrorelix controls the secretion of gonadotropins (LH and FSH).

Cetrorelix dose-dependently inhibits the secretion of LH and FSH from the pituitary gland. The onset of suppression is virtually immediate and is maintained by continuous treatment, without initial stimulatory effect.

In females, cetrorelix delays the LH surge and consequently ovulation. In women undergoing ovarian stimulation the duration of action of cetrorelix is dose dependent. Following a single dose of 3 mg of cetrorelix a duration of action of at least 4 days has been evaluated. On day 4 the suppression was approximately 70%. At a dose of 0.25 mg per injection repeated injections every 24 hours will maintain the effect of cetrorelix.

In animals as well as in humans, the antagonistic hormonal effects of cetrorelix were fully reversible after termination of treatment.

5.2 Pharmacokinetic properties

The absolute bioavailability of cetrorelix after subcutaneous administration is about 85%.

The total plasma clearance and the renal clearance are 1.2 ml x min^{-1} x kg^{-1} and 0.1 ml x min^{-1} x kg^{-1} , respectively. The volume of distribution ($V_{d,area}$) is 1.1 l x kg^{-1}. The mean terminal half-lives following intravenous and subcutaneous administration are about 12 h and 30 h, respectively, demonstrating the effect of absorption processes at the injection site. The subcutaneous administration of single doses (0.25 mg to 3 mg cetrorelix) and also daily dosing over 14 days show linear kinetics.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

No target organ toxicity could be observed from acute, subacute and chronic toxicity studies in rats and dogs following subcutaneous administration of cetrorelix. No signs of drug-related local irritation or incompatibility were noted in dogs after intravenous, intra-arterial and paravenous injection when cetrorelix was administered in doses clearly above the intended clinical use in man.

Cetrorelix showed no mutagenic or clastogenic potential in gene and chromosome mutation assays.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:

Mannitol

Solvent:

Water for Injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6

6.3 Shelf life

2 years.

The solution should be used immediately after preparation.

6.4 Special precautions for storage

Do not store above 25 °C. Keep the vial(s) in the outer carton in order to protect from light.

6.5 Nature and contents of container

Packs with 1 or 7 Type I glass vials each containing 55.7 mg powder for solution for injection sealed with a rubber stopper.

Additionally for each vial the packs contain:

1 pre-filled syringe (Type I glass cartridge closed with rubber stoppers) with 1 ml solvent for parenteral use
1 injection needle (20 gauge)
1 hypodermic injection needle (27 gauge)
2 alcohol swabs.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Cetrotide 0.25 mg should only be reconstituted with the solvent provided, using a gentle, swirling motion. Vigorous shaking with bubble formation should be avoided.

The reconstituted solution is without particles and clear. Do not use if the solution contains particles or if the solution is not clear.

Withdraw the entire contents of the vial. This ensures a delivery to the patient of a dose of at least 0.23 mg cetrorelix.

The solution should be used immediately after reconstitution.

The injection site should be varied daily.

7. MARKETING AUTHORISATION HOLDER

Serono Europe Limited
56 Marsh Wall
London E14 9TP
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/100/001
EU/1/99/100/002

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

13 April 1999
Date of last renewal: 15 April 2004

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

Cetrotide 3 mg powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 vial contains:
3.12 - 3.24 mg cetrorelix acetate equivalent to 3 mg cetrorelix.

After reconstitution with the solvent provided, the concentration of cetrorelix is 1 mg/ml.

Excipients: 164.40 mg mannitol.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection

Appearance of the powder: white lyophilized pellet
Appearance of the solvent: clear colourless solution

The pH of the reconstituted solution is 4.0 – 6.0

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prevention of premature ovulation in patients undergoing a controlled ovarian stimulation, followed by oocyte pick-up and assisted reproductive techniques.

In clinical trials Cetrotide 3 mg was used with human menopausal gonadotropin (HMG), however, limited experience with recombinant FSH suggested similar efficacy.

4.2 Posology and method of administration

Cetrotide 3 mg should only be prescribed by a specialist experienced in this field.

Cetrotide 3 mg is for subcutaneous injection into the lower abdominal wall.

The first administration of Cetrotide should be performed under the supervision of a physician and under conditions where treatment of possible pseudo-allergic reactions is immediately available. The following injections may be self-administered as long as the patient is made aware of the signs and symptoms that may indicate hypersensitivity, the consequences of such a reaction and the need for immediate medical intervention.

The contents of 1 vial (3 mg cetrorelix) are to be administered on day 7 of ovarian stimulation (approximately 132 to 144 hours after start of ovarian stimulation) with urinary or recombinant gonadotropins. Following the first administration, it is advised that the patient be kept under medical supervision for 30 minutes to ensure there is no allergic/pseudo-allergic reaction reaction to the injection. Facilities for the treatment of such reactions should be immediately available.

If the follicle growth does not allow ovulation induction on the fifth day after injection of Cetrotide 3 mg, additionally 0.25 mg cetrorelix (Cetrotide 0.25 mg) should be administered once daily beginning 96 hours after the injection of Cetrotide 3 mg until the day of ovulation induction.

For instructions on preparation , see section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance or any structural analogue of GnRH, extrinsic peptide hormones or to any of the excipients .
- Pregnancy, and lactation.
- Postmenopausal women.
- Patients with moderate and severe renal and hepatic impairment.

4.4 Special warnings and precautions for use

Special care should be taken in women with signs and symptoms of active allergic conditions or known history of allergic predisposition. Treatment with Cetrotide is not advised in women with severe allergic conditions.

During or following ovarian stimulation an ovarian hyperstimulation syndrome can occur. This event must be considered as an intrinsic risk of the stimulation procedure with gonadotropins.

An ovarian hyperstimulation syndrome should be treated symptomatically, e.g. with rest, intravenous electrolytes/colloids and heparin therapy.

Luteal phase support should be given according to the reproductive medical centre´s practice.

There is limited experience up to now with the administration of Cetrotide 3 mg during a repeated ovarian stimulation procedure. Therefore Cetrotide 3 mg should be used in repeated cycles only after a careful risk/benefit evaluation.

4.5 Interaction with other medicinal products and other forms of interaction

In vitro investigations have shown that interactions are unlikely with medications that are metabolised by cytochrome P450 or glucuronised or conjugated in some other way. However, interactions with commonly used medicinal products, including products that may induce histamine release in susceptible individuals, may occur.

4.6 Pregnancy and lactation

Cetrotide 3 mg is not intended to be used during pregnancy and lactation (see section 4.3).

Studies in animals have indicated that cetrorelix exerts a dose related influence on fertility, reproductive performance and pregnancy. No teratogenic effects occurred when the drug was administered during the sensitive phase of gestation.

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Due to its pharmacological profile cetrorelix is unlikely to impair the patient’s ability to drive or to operate machinery.

4.8 Undesirable effects

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Immune system disorders	Rare (≥1/10,000, <1/1,000)	Rare cases of hypersensitivity reactions including pseudo-allergic/anaphylactoid reactions have also been reported
Nervous system disorders	Uncommon (≥1/1,000, <1/100)	Headache
Gastrointestinal disorders	Uncommon (≥1/1,000, <1/100)	Nausea
Reproductive system and breast disorders	Common (≥1/100, <1/10)	Mild to moderate ovarian hyperstimulation syndrome (WHO grade I or II) can occur which is an intrinsic risk of the stimulation procedure (see section 4.4).
	Uncommon (≥1/1,000, <1/100)	Severe ovarian hyperstimulation syndrome (WHO grade III)
General disorders and administration site conditions	Common (≥1/100, <1/10)	Local reactions at the injection site (e.g. erythema, swelling and pruritus) have been reported. Usually they were transient in nature and mild intensity. The frequency as reported in clinical trials was 8.0%.

4.9 Overdose

Overdosage in humans may result in a prolonged duration of action but is unlikely to be associated with acute toxic effects.

In acute toxicity studies in rodents non-specific toxic symptoms were observed after intraperitoneal administration of cetrorelix doses more than 200 times higher than the pharmacologically effective dose after subcutaneous administration.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: LHRH-Antagonist, ATC code: H01CC02.

Cetrorelix is a luteinising hormone releasing hormone (LHRH) antagonist. LHRH binds to membrane receptors on pituitary cells. Cetrorelix competes with the binding of endogenous LHRH to these receptors. Due to this mode of action, cetrorelix controls the secretion of gonadotropins (LH and FSH).

Cetrorelix dose-dependently inhibits the secretion of LH and FSH from the pituitary gland. The onset of suppression is virtually immediate and is maintained by continuous treatment, without initial stimulatory effect.

In females, cetrorelix delays the LH surge and consequently ovulation.

In women undergoing ovarian stimulation the duration of action of cetrorelix is dose dependent. Following a single dose of 3 mg of cetrorelix a duration of action of at least 4 days has been evaluated. On day 4 the suppression was approximately 70%. At a dose of 0.25 mg per injection repeated injections every 24 hours will maintain the effect of cetrorelix.

In animals as well as in humans, the antagonistic hormonal effects of cetrorelix were fully reversible after termination of treatment.

5.2 Pharmacokinetic properties

The absolute bioavailability of cetrorelix after subcutaneous administration is about 85%.

The total plasma clearance and the renal clearance are 1.2 ml x min^{-1} x kg^{-1} and 0.1 ml x min^{-1} x kg^{-1} , respectively. The volume of distribution ($V_{d,area}$) is 1.1 l x kg^{-1}. The mean terminal half-lives following intravenous and subcutaneous administration are about 12 h and 30 h, respectively, demonstrating the effect of absorption processes at the injection site. The subcutaneous administration of single doses (0.25 mg to 3 mg cetrorelix) and also daily dosing over 14 days show linear kinetics.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard to humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

No target organ toxicity could be observed from acute, subacute and chronic toxicity studies in rats and dogs following subcutaneous administration of cetrorelix. No signs of drug-related local irritation or incompatibility were noted in dogs after intravenous, intra-arterial and paravenous injection when cetrorelix was administered in doses clearly above the intended clinical use in man.

Cetrorelix showed no mutagenic or clastogenic potential in gene and chromosome mutation assays.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:

Mannitol

Solvent:

Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

2 years.

The solution should be used immediately after preparation.

6.4 Special precautions for storage

Do not store above 25 °C. Keep the vial in the outer carton in order to protect from light.

6.5 Nature and contents of container

Pack with 1 Type I glass vial containing 167.7 mg powder for solution for injection sealed with a rubber stopper.

Additionally the pack contains:

1 pre-filled syringe (Type I glass cartridge closed with rubber stoppers) with 3 ml solvent for parenteral use
1 injection needle (20 gauge)
1 hypodermic injection needle (27 gauge)
2 alcohol swabs.

6.6 Special precautions for disposal and other handling

Cetrotide 3 mg should only be reconstituted with the solvent provided, using a gentle, swirling motion. Vigorous shaking with bubble formation should be avoided.

The reconstituted solution is without particles and clear. Do not use if the solution contains particles or if the solution is not clear.

Withdraw the entire contents of the vial. This ensures a delivery to the patient of a dose of at least 2.82 mg cetrorelix.

The solution should be used immediately after reconstitution.

7. MARKETING AUTHORISATION HOLDER

Serono Europe Limited
56 Marsh Wall
London E14 9TP
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/100/003

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

13 April 1999
Date of last renewal: 15 April 2004

10. DATE OF REVISION OF THE TEXT

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDERRESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Baxter Oncology GmbH
Kantstraße 2
D-33790 Halle
Germany

Æterna Zentaris GmbH
Weismüllerstraße 50
D-60314 Frankfurt
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to medical prescription.

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BOX OF 1 VIAL AND 1 PRE-FILLED SYRINGE

1. NAME OF THE MEDICINAL PRODUCT

Cetrotide 0.25 mg, powder and solvent for solution for injection.
cetrorelix

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial with 55.7 mg powder contains:
0.26 – 0.27 mg cetrorelix acetate equivalent to 0.25 mg cetrorelix.

3. LIST OF EXCIPIENTS

Excipient: Mannitol.
1 pre-filled syringe with solvent contains: 1 ml water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial with powder for solution for injection.
1 pre-filled syringe with solvent for parenteral use.
Additionally, the pack contains:
1 injection needle (20 gauge)
1 hypodermic injection needle (27 gauge)
2 alcohol swabs.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C. Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Serono Europe Limited
56 Marsh Wall
London E14 9TP
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/100/001

13. BATCH NUMBER

Batch:
Solvent Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

cetrotide 0.25 mg

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BOX OF 7 VIAL AND 7 PRE-FILLED SYRINGE

1. NAME OF THE MEDICINAL PRODUCT

Cetrotide 0.25 mg, powder and solvent for solution for injection.
cetrorelix

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial with 55.7 mg powder contains:
0.26 – 0.27 mg cetrorelix acetate equivalent to 0.25 mg cetrorelix.

3. LIST OF EXCIPIENTS

Excipient: Mannitol.
1 pre-filled syringe with solvent contains: 1 ml water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

7 vials with powder for solution for injection.
7 pre-filled syringes with solvent for parenteral use.
Additionally, the pack contains :
7 injection needle (20 gauge)
7 hypodermic injection needle (27 gauge)
14 alcohol swabs.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C. Keep the vial(s) in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Serono Europe Limited
56 Marsh Wall
London E14 9TP
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/100/002

13. BATCH NUMBER

Batch:
SolventBatch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

cetrotide 0.25mg

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

CETROTIDE 0.25 MG VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Cetrotide 0.25 mg powder for solution for injection
cetrorelix
Subcutaneous use.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

55.7 mg/vial

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SOLVENT PRE-FILLED SYRINGE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Water for Injections
Solvent for use with Cetrotide 0.25 mg

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 ml/pre-filled syringe

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BOX OF 1 VIAL AND 1 PRE-FILLED SYRINGE

1. NAME OF THE MEDICINAL PRODUCT

Cetrotide 3 mg, powder and solvent for solution for injection.
cetrorelix

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial with 167.7 mg powder contains:
3.12 – 3.24 mg cetrorelix acetate equivalent to 3 mg cetrorelix.

3. LIST OF EXCIPIENTS

Excipient: Mannitol.
1 pre-filled syringe with solvent contains: 3 ml water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial with powder for solution for injection.
1 pre-filled syringe with solvent for parenteral use.
Additionally, the pack contains:
1 injection needle (20 gauge)
1 hypodermic injection needle (27 gauge)
2 alcohol swabs.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C. Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Serono Europe Limited
56 Marsh Wall
London E14 9TP
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/100/003

13. BATCH NUMBER

Batch
Solvent Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

cetrotide 3mg

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

CETROTIDE 3 MG VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Cetrotide 3 mg powder for solution for injection
cetrorelix
Subcutaneous use.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

167.7 mg/vial

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SOLVENT PRE-FILLED SYRINGE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Water for Injections
Solvent for use with Cetrotide 3 mg

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml/pre-filled syringe

6. OTHER

B. PACKAGE LEAFLET

PACKAGE LEAFLET : INFORMATION FOR THE USER

Cetrotide 0.25mg powder and solvent for solution for injection

Cetrorelix acetate

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT CETROTIDE IS AND WHAT IT IS USED FOR

Cetrotide 0.25 mg inhibits the effects of a natural hormone, called luteinising hormone releasing hormone (LHRH). LHRH regulates the secretion of another hormone, called luteinising hormone (LH), which induces ovulation during the menstrual cycle. Cetrotide 0.25 mg inhibits premature ovulation which is undesirable during hormone treatment for ovarian stimulation as only mature egg cells are suitable for fertilisation.

Therapeutic indications

Cetrotide 0.25 mg is used to prevent premature ovulation during a controlled ovarian stimulation, followed by oocyte pick-up and assisted reproductive techniques.

In clinical trials Cetrotide 0.25 mg was used with human menopausal gonadotropin (HMG), however, limited experience with recombinant follicle stimulating hormone (FSH) suggested similar efficacy. HMG and FSH are hormones promoting egg maturation.

2. BEFORE YOU USE CETROTIDE

Do not use Cetrotide

- if you are allergic (hypersensitive) to cetrorelix acetate, exogenous peptide hormones (medicines similar to Cetrotide 0.25 mg) or any of the other ingredients.
- if you are pregnant or breast-feeding
- if you have already reached your menopause
- if you have a moderate or severe kidney or liver disease.

Take special care with Cetrotide

Special care should be taken in women with an active allergic condition or a known history of allergy. Since treatment with Cetrotide is not advised in women with severe allergic conditions it is important that you inform your doctor of any allergies.

During or following hormonal stimulation of the ovaries an ovarian hyperstimulation syndrome can occur. This event is related to the stimulation procedure with gonadotropins (hormones promoting egg maturation). For symptoms and suitable measures please refer to the Patient Information Leaflet of the gonadotropin-containing medicine prescribed for you.

Luteal phase support (a measure to support the onset of pregnancy) should be given according to the reproductive medical centre´s practice.

There is limited experience up to now with the administration of Cetrotide 0.25 mg during a repeated ovarian stimulation procedure. Therefore you should use Cetrotide 0.25 mg in repeated cycles only after a careful risk/benefit evaluation by your doctor.

Using other medicines

Experimental investigations have shown that interactions are unlikely with medications that are metabolised in the liver. However, the possibility of interactions with commonly used medicinal products cannot entirely be excluded.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Pregnancy and breast-feeding:

You should not use Cetrotide 0.25 mg if you are already pregnant, or suspect that you might be pregnant, or if you are breast-feeding.

3. HOW TO USE CETROTIDE

Always use cetrotide exactly as your doctor has told you. You should check with your doctor if you are not sure. The following statements apply to Cetrotide 0.25 mg unless otherwise prescribed by your doctor. Please observe these instructions for use, otherwise you will not fully benefit from Cetrotide 0.25 mg.

The contents of one vial (0.25 mg Cetrorelix) are to be administered once daily, at 24 h intervals, either in the morning or in the evening.

Administration in the morning: Treatment with Cetrotide 0.25 mg should begin on day 5 or 6 of ovarian stimulation (approximately 96 to 120 hours after start of ovarian stimulation) with urinary or recombinant gonadotropins and is to be continued throughout the gonadotropin treatment period including the day of ovulation induction.

Administration in the evening: Treatment with Cetrotide 0.25 mg should begin on day 5 of ovarian stimulation (approximately 96 to 108 hours after start of ovarian stimulation) with urinary or recombinant gonadotropins and is to be continued throughout the gonadotropin treatment period until the evening prior to the day of ovulation induction.

Route of administration

Cetrotide is intended for subcutaneous use, that means given by injection just under the skin. It is for single use only.

The first injection of Cetrotide should be supervised by your doctor. You can carry out the following injections yourself as long as you have been made aware by your doctor of the symptoms that may indicate allergy, the consequences of such a reaction and the need for immediate treatment.

Cetrotide 0.25 mg is for injection under the skin of the lower abdominal wall, preferably around the navel. To minimise local irritation, please select a different injection site each day.

Dissolve Cetrotide 0.25 mg powder only with the water contained in the pre-filled syringe. Do not use a Cetrotide 0.25 mg solution if it contains particles or if it is not clear.

Before you administer Cetrotide yourself, please read the following instructions carefully

1. Wash your hands. It is important that your hands and all items you use are as clean as possible.

2. Lay out on a clean surface everything you need (one vial, one pre-filled syringe, one injection needle with a yellow mark, one injection needle with a grey mark and two alcohol swabs).

3. Flip off the plastic cover of the vial. Wipe the aluminium ring and the rubber stopper with an alcohol swab.

4. Take the injection needle with the yellow mark and remove the wrapping. Take the pre-filled syringe and remove the cover. Put the needle on the syringe and remove the cover of the needle.

5. Push the needle through the centre of the rubber stopper of the vial. Inject the water into the vial by slowly pushing the plunger of the syringe.

6. Leave the syringe on the vial. Gently agitate the vial until the solution is clear and without residue. Avoid forming bubbles during dissolution.

7. Draw the whole contents of the vial into the syringe. If solution is left in the vial, invert the vial, pull back the needle until the opening of the needle is just inside the stopper. If you look from the side through the gap in the stopper, you can control the movement of the needle and the liquid. It is important to withdraw the entire contents of the vial.

8. Detach the syringe from the needle and lay down the syringe. Take the injection needle with the grey mark and remove its wrapping. Put the needle on the syringe and remove the cover of the needle.

9. Invert the syringe and push the plunger until all air bubbles have been expelled. Do not touch the needle or allow the needle to touch any surface.

10. Choose an injection site at the lower abdominal wall, preferably around the navel. Take the second alcohol swab and clean the skin at the injection site. Hold the syringe in one hand. Gently pinch up the skin surrounding the site of injection and hold firmly with the other hand.

11. Hold the syringe as you would hold a pencil, insert the needle completely into the skin at an angle of about 45 degree.

12. Once the needle has been inserted completely, release your grasp of the skin.

13. Pull back gently the plunger of the syringe. If blood appears continue as described in step 14. If no blood appears, inject the solution slowly by pushing the plunger gently forward. After all of the solution is injected, withdraw the needle slowly, applying gentle pressure with the alcohol swab on the skin where the needle was inserted. Withdraw the needle at the same angle as it was inserted.

14. If blood appears, withdraw the needle with the syringe and gently apply pressure to the injection site. Do not use this solution but empty the syringe in a sink. Start again with step 1.

15. Use the syringe and needles only once. Dispose of the syringe and needles immediately after use (put the covers on the needles to avoid injury).

If you use more Cetrotide than you should

Overdosage of Cetrotide 0.25 mg may result in a prolonged duration of action but is unlikely to be associated with acute toxic effects. Therefore, in case of overdosage no specific measures are required.

If you forget to take Cetrotide:

Do not take a double dose to make up for a forgotten dose, please contact your doctor.

Ideally Cetrotide 0.25 mg should be administered at 24 hours intervals. But if you missed to administer Cetrotide 0.25 mg at the right time it is no problem to administer this dose at a different time of the same day.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Cetrotide can cause side effects, although not everybody gets them.

Mild and transient reactions may occur at the injection site like reddening, itching, and swelling. These problems may affect between 1 and 10 patients out of 100 treated.

Rare cases of severe generalised allergic reactions have also been reported (less than 1 in 1000 patients).

Occasionally systemic side effects, like nausea and headache have been reported (less than 1 in 100 patients). In addition, a single case of pruritus has been reported during treatment with Cetrorelix.

Occasionally, stimulation of ovaries with gonadotropins (hormones promoting egg maturation) may lead to a so-called ovarian hyperstimulation syndrome (OHSS). Symptoms like abdominal pain, tension, nausea, vomiting, diarrhoea and breathing difficulties may indicate an OHSS. These problems may affect between 1 and 10 patients out of 100 treated**.** Please inform your doctor immediately, if you feel such symptoms.

If any of the side effects gets serious, or if you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. HOW TO STORE CETROTIDE

Keep out of the reach and sight of children.

Do not store above 25°C.

Keep the vial in the outer carton in order to protect from light.

Do not use Cetrotide after the expiry date which is stated on the vial after EXP. The expiry date refers to the last day of that month.
The Cetrotide 0.25 mg powder in the vial and the solvent in the pre-filled syringe have the same expiry date. It is printed on the labels and on the carton.
The solution should be used immediately after preparation.

Do not use Cetrotide if the white pellet in the vial has changed in aspect or colour, or if the solvent solution in the vial is no longer clear and colourless or if it contains particles.

If you have any further questions please consult your doctor or pharmacist.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Cetrotide contains

The active substance is cetrorelix acetate 0.26 – 0.27 mg, equivalent to 0.25 mg cetrorelix.

The other ingredient is mannitol.

The solvent is Water for Injections.

What Cetrotide looks like and contents of the pack

Cetrotide 0.25 mg is a powder for solution for injection. It is available in packs of one or seven vials.

Additionally, for each vial the packs contain

- one pre-filled syringe with solvent (water for injections) for parenteral use for dissolving the powder in the vial
- one injection needle with a yellow mark for injecting the water into the vial and withdrawing the solution from the vial
- one injection needle with a grey mark for injecting the solution
- two alcohol swabs for cleaning purposes.

Marketing Authorisation Holder

Serono Europe Limited, 56 Marsh Wall, London E14 9TP,United Kingdom

Manufacturer

Baxter Oncology GmBH, Kantstrasse 2, D-33790 Halle, Germany
or
Æterna Zentaris GmbH, Weismüllerstrasse 50, D-60314 Frankfurt, Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

België/Belgique/Belgien
Serono Benelux BV
Heizel Esplanade Heysel - b11
B -1020 Brussel/Bruxelles/Brüssel
Tel./Tél.: +32 2 481 75 80

Luxembourg/Luxemburg
Serono Benelux BV
Esplanade Heysel - b11
B - 1020 Bruxelles/Brüssel
Belgique/Belgien
Tél./Tel.: +32 2 48175 80

България
Serono Austria GmbH
Floridsdorfer Hauptstraße 1
A-1210 Виена
Австрия
Тел.: + 43 1 6047690

Magyarország
Serono Austria GmbH
Floridsdorfer Hauptstraße 1
A-1210 Bécs
Ausztria
Tel: + 43 1 6047690

Česká republika
Serono Austria GmbH
Floridsdorfer Hauptstraße 1
A-1210 Vídeň
Rakousko
Tel: + 43 1 6047690

Danmark
Serono Nordic
Strandvejen 102 B, 4, th.
DK-2900 Hellerup
Tlf: +45-35 25 35 50

Deutschland
Serono GmbH
Freisinger Straße 5
D-85716 Unterschleißheim
Tel: +49-89-321 56 0

Eesti
Serono Austria GmbH
Floridsdorfer Hauptstraße 1
A-1210 Viin
Austria
Tel: + 43 1 6047690

Ελλάδα
Serono Hellas A.E.
Κηφισίας 41-45, Κτήριο Β
GR-151 23 Μαρούσι
Αθήνα
Τηλ: +30-210-616 51 00

España
Serono España S.A.
María de Molina, 40
E-28006 Madrid
Línea de Información Serono: 900 200 400
Tel: +34-91-745 44 00

France
Serono France S.A.
738, rue Yves Kermen
F-92658 Boulogne Cedex
Numéro vert : 0.800.888.024
Tél: +33-1-47 61 13 13

Ireland
Serono Ltd.
Bedfont Cross, Stanwell Road
Feltham, Middlesex TW 14 8NX
United Kingdom
Tel: +44-208-818-7200

Malta
Cherubino LTD
Delf Building
Sliema Road
MT-GZR 06 Gzira Malta
Tel: +356-21-343270/1/2/3/4

Nederland
Serono Benelux BV
Alexanderstraat 3-5
NL-2514 JL Den Haag
Tel: +31-70-30 25 700

Norge
Serono Nordic
Luhrtoppen 2
N-1470 Lørenskog
Tlf: +47-67-90 35 90

Österreich
Serono Austria GmbH
Floridsdorfer Hauptstraße 1
A-1210 Wien
Tel: + 43 1 6047690

Polska
Serono Austria GmbH
Floridsdorfer Hauptstraße 1
A-1210 Wiedeń
Austria
Tel: + 43 1 6047690

Portugal
Serono Portugal Lda
Rua Tierno Galvan, n° 16B
Amoreiras, Torre 3, Piso 16, Esc.1
P-1070-274 Lisboa
Linha de informação Serono: 800 834 181
Tel: +351-21-384 92 10

România
Serono Austria GmbH
Floridsdorfer Hauptstraße 1
A-1210 Viena
Austria
Tel: +43 1 6047690

Slovenija
Serono Austria GmbH
Floridsdorfer Hauptstraße 1
A-1210 Dunaj
Avstrija
Tel: + 43 1 6047690

Ísland
Gróco ehf.
Þverholti 14
IS-105 Reykjavík
Sími: +354-568-8533

Italia
Industria Farmaceutica Serono S.p.A.
Via Casilina 125
I-00176 Roma
Tel: +39-06-70 38 41

Κύπρος
Akis Panayiotou & Son LTD
Γιάννου Κρανιδιώτη 4
CY-225 78, Λευκωσία
Τηλ: +357-22677038

Latvija
Serono Austria GmbH
Floridsdorfer Hauptstraße 1
A-1210 Vīne
Austrija
Tel: + 43 1 6047690

Lietuva
Serono Austria GmbH
Floridsdorfer Hauptstraße 1
A-1210 Viena
Austrija
Tel: + 43 1 6047690

This leaflet was last approved on

Slovenská republika
Serono Austria GmbH
Floridsdorfer Hauptstraße 1
A-1210 Viedeň
Rakúsko
Tel: + 43 1 6047690

Suomi/Finland
Serono Nordic
Rajatorpantie 41B
FIN-01640 Vantaa
Puh/Tel: +358-9-85 20 20 20

Sverige
Serono Nordic AB
S-195 87 Stockholm
Tel: +46-8-562 445 00

United Kingdom
Serono Ltd.
Bedfont Cross, Stanwell Road
Feltham, Middlesex TW 14 8NX - UK
Tel: +44-208-818-7200

PACKAGE LEAFLET : INFORMATION FOR THE USER

Cetrotide 3mg powder and solvent for solution for injection

Cetrorelix acetate

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT CETROTIDE IS AND WHAT IT IS USED FOR

Cetrotide 3 mg inhibits the effects of a natural hormone, called luteinising hormone releasing hormone (LHRH). LHRH regulates the secretion of another hormone, called luteinising hormone (LH), which induces ovulation during the menstrual cycle. Cetrotide 3 mg inhibits premature ovulation which is undesirable during hormone treatment for ovarian stimulation as only mature egg cells are suitable for fertilisation.

Therapeutic indications

Cetrotide 3 mg is used to prevent premature ovulation during a controlled ovarian stimulation, followed by oocyte pick-up and assisted reproductive techniques.

In clinical trials Cetrotide 3 mg was used with human menopausal gonadotropin (HMG), however, limited experience with recombinant follicle stimulating hormone (FSH) suggested similar efficacy. HMG and FSH are hormones promoting egg maturation.

2. BEFORE YOU USE CETROTIDE

Do not use Cetrotide:

- if you are allergic (hypersensitive) to cetrorelix acetate, exogenous peptide hormones (medicines similar to Cetrotide 3 mg), or any of the other ingredients.
- if you are pregnant or breast-feeding
- if you have already reached your menopause
- if you have a moderate or severe kidney or liver disease.

Take special care with Cetrotide:

Special care should be taken in women with an active allergic condition or a known history of allergy. Since treatment with Cetrotide is not advised in women with severe allergic conditions it is important that you inform your doctor of any allergies.

During or following hormonal stimulation of the ovaries an ovarian hyperstimulation syndrome can occur. This event is related to the stimulation procedure with gonadotropins (hormones promoting egg maturation). For symptoms and suitable measures please refer to the Patient Information Leaflet of the gonadotropin-containing medicine prescribed for you.

Luteal phase support (a measure to support the onset of pregnancy) should be given according to the reproductive medical centre´s practice.

There is limited experience up to now with the administration of Cetrotide 3 mg during a repeated ovarian stimulation procedure. Therefore you should use Cetrotide 3 mg in repeated cycles only after a careful risk/benefit evaluation by your doctor.

Using other medicines

Experimental investigations have shown that interactions are unlikely with medications that are metabolised in the liver. However, the possibility of interactions with commonly used medicinal products cannot entirely be excluded.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Pregnancy and breast-feeding:

You should not use Cetrotide 3 mg if you are already pregnant, or suspect that you might be pregnant, or if you are breast-feeding.

3. HOW TO USE CETROTIDE

Always use cetrtide exactly as your doctor has told you. You should check with your doctor if you are not sure. The following statements apply to Cetrotide 3 mg unless otherwise prescribed by your doctor. Please observe these instructions for use, otherwise you will not fully benefit from Cetrotide 3 mg.

The contents of 1 vial (3 mg cetrorelix) are to be administered on day 7 of ovarian stimulation (approximately 132 to 144 hours after start of ovarian stimulation) with urinary or recombinant gonadotropins.

A single dose of Cetrotide 3 mg results in a duration of action of at least 4 days. If the follicle growth does not allow ovulation induction on the fifth day after injection of Cetrotide 3 mg, additionally 0.25 mg cetrorelix (Cetrotide 0.25 mg) should be administered once daily beginning 96 hours after the injection of Cetrotide 3 mg until the day of ovulation induction.

Route of administration

Cetrotide is intended for subcutaneous use, that means given by injection just under the skin. It is for single use only.

The first injection of Cetrotide should be supervised by your doctor. You can carry out the following injections yourself as long as you have been made aware by your doctor of the symptoms that may indicate allergy, the consequences of such a reaction and the need for immediate treatment.

Cetrotide 3 mg is for injection under the skin of the lower abdominal wall, preferably around the navel.

Dissolve Cetrotide 3 mg powder only with the water contained in the pre-filled syringe. Do not use a Cetrotide 3 mg solution if it contains particles or if it is not clear.

Before you administer Cetrotide yourself, please read the following instructions carefully

1. Wash your hands. It is important that your hands and all items you use are as clean as possible.

2. Lay out on a clean surface everything you need (one vial, one pre-filled syringe, one injection needle with a yellow mark, one injection needle with a grey mark and two alcohol swabs).

3. Flip off the plastic cover of the vial. Wipe the aluminium ring and the rubber stopper with an alcohol swab.

4. Take the injection needle with the yellow mark and remove the wrapping. Take the pre-filled syringe and remove the cover. Put the needle on the syringe and remove the cover of the needle.

5. Push the needle through the centre of the rubber stopper of the vial. Inject the water into the vial by slowly pushing the plunger of the syringe.

6. Leave the syringe on the vial. Gently agitate the vial until the solution is clear and without residue. Avoid forming bubbles during dissolution.

7. Draw the whole contents of the vial into the syringe. If solution is left in the vial, invert the vial, pull back the needle until the opening of the needle is just inside the stopper. If you look from the side through the gap in the stopper, you can control the movement of the needle and the liquid. It is important to withdraw the entire contents of the vial.

8. Detach the syringe from the needle and lay down the syringe. Take the injection needle with the grey mark and remove its wrapping. Put the needle on the syringe and remove the cover of the needle.

9. Invert the syringe and push the plunger until all air bubbles have been expelled. Do not touch the needle or allow the needle to touch any surface.

10. Choose an injection site at the lower abdominal wall, preferably around the navel. Take the second alcohol swab and clean the skin at the injection site. Hold the syringe in one hand. Gently pinch up the skin surrounding the site of injection and hold firmly with the other hand.

11. Hold the syringe as you would hold a pencil, insert the needle completely into the skin at an angle of about 45 degree.

12. Once the needle has been inserted completely, release your grasp of the skin.

13. Pull back gently the plunger of the syringe. If blood appears continue as described in step 14. If no blood appears, inject the solution slowly by pushing the plunger gently forward. After all of the solution is injected, withdraw the needle slowly, applying gentle pressure with the alcohol swab on the skin where the needle was inserted. Withdraw the needle at the same angle as it was inserted.

14. If blood appears, withdraw the needle with the syringe and gently apply pressure to the injection site. Do not use this solution but empty the syringe in a sink.

15. Use the syringe and needles only once. Dispose of the syringe and needles immediately after use (put the covers on the needles to avoid injury).

If you use more Cetrotide than you should

Overdosage of Cetrotide 3 mg may result in a prolonged duration of action but is unlikely to be associated with acute toxic effects. Therefore, in case of overdosage no specific measures are required.

If you forget to take Cetrotide:

Do not take a double dose to make up for a forgotten dose, please contact your doctor.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Cetrotide can cause side effects, although not everybody gets them.

Mild and transient reactions may occur at the injection site like reddening, itching, and swelling. These problems may affect between 1 and 10 patients out of 100 treated.

Rare cases of severe generalised allergic reactions have also been reported (less than 1 in 1000 patients).

Occasionally systemic side effects, like nausea and headache have been reported (less than 1 patient in 100). In addition, a single case of pruritus has been reported during treatment with Cetrorelix.

Occasionally, stimulation of ovaries with gonadotropins (hormones promoting egg maturation) may lead to a so-called ovarian hyperstimulation syndrome (OHSS). Symptoms like abdominal pain, tension, nausea, vomiting, diarrhoea and breathing difficulties may indicate an OHSS. These problems may affect between 1 and 10 patients out of 100 treated.
Please inform your doctor immediately, if you feel such symptoms.

If you notice any side effects gets serious, or if you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. HOW TO STORE CETROTIDE

Keep out of the reach and sight of children.

Do not store above 25°C.

Keep the vial in the outer carton in order to protect from light.

Do not use Cetrotide after the expiry date which is stated on the vial after EXP. The expiry date refers to the last day of that month.

The Cetrotide 3 mg powder in the vial and the solvent in the pre-filled syringe have the same expiry date. It is printed on the labels and on the carton.
The solution should be used immediately after preparation.

Do not use Cetrotide if the white pellet in the vial has changed in aspect or colour, or if the solvent solution in the vial is no longer clear and colourless or if it contains particles.

If you have any further questions please consult your doctor or pharmacist.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help protect the environment.

6. FURTHER INFORMATION

What Cetrotide contains

The active substance is cetrorelix acetate 3.12 – 3.24 mg, equivalent to 3 mg cetrorelix.

The other ingredient is mannitol.

The solvent is Water for Injections.

What Cetrotide looks like and contents of the pack

Cetrotide 3mg is a powder for solution for injection. It is available in a pack with one vial.

Additionally, for each vial the packs contain

- one pre-filled syringe with solvent (water for injections) for parenteral use for dissolving the powder in the vial
- one injection needle with a yellow mark for injecting the water into the vial and withdrawing the solution from the vial
- one injection needle with a grey mark for injecting the solution
- two alcohol swabs for cleaning purposes.

Marketing Authorisation Holder

Serono Europe Limited, 56 Marsh Wall, London E14 9TP,United Kingdom

Manufacturer

Baxter Oncology GmbH, Kantstrasse 2, D-33790 Halle, Germany
or
Æterna Zentaris GmbH, Weismüllerstrasse 50, D-60314 Frankfurt, Germany

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

België/Belgique/Belgien
Serono Benelux BV
Heizel Esplanade Heysel - b11
B -1020 Brussel/Bruxelles/Brüssel
Tel./Tél.: +32 2 481 75 80

Luxembourg/Luxemburg
Serono Benelux BV
Esplanade Heysel - b11
B - 1020 Bruxelles/Brüssel
Belgique/Belgien
Tél./Tel.: +32 2 48175 80

България
Serono Austria GmbH
Floridsdorfer Hauptstraße 1
A-1210 Виена
Австрия
Тел.: + 43 1 6047690

Magyarország
Serono Austria GmbH
Floridsdorfer Hauptstraße 1
A-1210 Bécs
Ausztria
Tel: + 43 1 6047690

Česká republika
Serono Austria GmbH
Floridsdorfer Hauptstraße 1
A-1210 Vídeň
Rakousko
Tel: + 43 1 6047690

Danmark
Serono Nordic
Strandvejen 102 B, 4, th.
DK-2900 Hellerup
Tlf: +45-35 25 35 50

Deutschland
Serono GmbH
Freisinger Straße 5
D-85716 Unterschleißheim
Tel: +49-89-321 56 0

Eesti
Serono Austria GmbH
Floridsdorfer Hauptstraße 1
A-1210 Viin
Austria
Tel: + 43 1 6047690

Ελλάδα
Serono Hellas A.E.
Κηφισίας 41-45, Κτήριο Β
GR-151 23 Μαρούσι
Αθήνα
Τηλ: +30-210-616 51 00

España
Serono España S.A.
María de Molina, 40
E-28006 Madrid
Línea de Información Serono: 900 200 400
Tel: +34-91-745 44 00

France
Serono France S.A.
738, rue Yves Kermen
F-92658 Boulogne Cedex
Numéro vert : 0.800.888.024
Tél: +33-1-47 61 13 13

Ireland
Serono Ltd.
Bedfont Cross, Stanwell Road
Feltham, Middlesex TW 14 8NX
United Kingdom
Tel: +44-208-818-7200

Malta
Cherubino LTD
Delf Building
Sliema Road
MT-GZR 06 Gzira Malta
Tel: +356-21-343270/1/2/3/4

Nederland
Serono Benelux BV
Alexanderstraat 3-5
NL-2514 JL Den Haag
Tel: +31-70-30 25 700

Norge
Serono Nordic
Luhrtoppen 2
N-1470 Lørenskog
Tlf: +47-67-90 35 90

Österreich
Serono Austria GmbH
Floridsdorfer Hauptstraße 1
A-1210 Wien
Tel: + 43 1 6047690

Polska
Serono Austria GmbH
Floridsdorfer Hauptstraße 1
A-1210 Wiedeń
Austria
Tel: + 43 1 6047690

Portugal
Serono Portugal Lda
Rua Tierno Galvan, n° 16B
Amoreiras, Torre 3, Piso 16, Esc.1
P-1070-274 Lisboa
Linha de informação Serono: 800 834 181
Tel: +351-21-384 92 10

România
Serono Austria GmbH
Floridsdorfer Hauptstraße 1
A-1210 Viena
Austria
Tel: +43 1 6047690

Slovenija
Serono Austria GmbH
Floridsdorfer Hauptstraße 1
A-1210 Dunaj
Avstrija
Tel: + 43 1 6047690

Ísland
Gróco ehf.
Þverholti 14
IS-105 Reykjavík
Sími: +354-568-8533

Italia
Industria Farmaceutica Serono S.p.A.
Via Casilina 125
I-00176 Roma
Tel: +39-06-70 38 41

Κύπρος
Akis Panayiotou & Son LTD
Γιάννου Κρανιδιώτη 4
CY-225 78, Λευκωσία
Τηλ: +357-22677038

Latvija
Serono Austria GmbH
Floridsdorfer Hauptstraße 1
A-1210 Vīne
Austrija
Tel: + 43 1 6047690

Lietuva
Serono Austria GmbH
Floridsdorfer Hauptstraße 1
A-1210 Viena
Austrija
Tel: + 43 1 6047690

This leaflet was last approved on

Slovenská republika
Serono Austria GmbH
Floridsdorfer Hauptstraße 1
A-1210 Viedeň
Rakúsko
Tel: + 43 1 6047690

Suomi/Finland
Serono Nordic
Rajatorpantie 41B
FIN-01640 Vantaa
Puh/Tel: +358-9-85 20 20 20

Sverige
Serono Nordic AB
S-195 87 Stockholm
Tel: +46-8-562 445 00

United Kingdom
Serono Ltd.
Bedfont Cross, Stanwell Road
Feltham, Middlesex TW 14 8NX - UK
Tel: +44-208-818-7200